UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,211	08/22/2006	Jean-Marie Buerstedde	P30753US00	5528

28381 7590 02/08/2008

ARNOLD & PORTER LLP
ATTN: IP DOCKETING DEPT.
555 TWELFTH STREET, N.W.
WASHINGTON, DC 20004-1206

EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
02/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,211	BUERSTEDDE ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-31,35 and 44-62* is/are pending in the application.

4a) Of the above claim(s) *30,57 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,31,35,44-56 and 58-61* is/are rejected.

7)☒ Claim(s) *59* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 August 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/14/2006 & 3/23/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response of November 21, 2007, to the Restriction Requirement dated September 21, 2007 has been entered. Claims 29-31 and 35 have been amended, and claims 1-28, 32-34 and 36-43 cancelled. Claims 44-62 have been newly added. Accordingly, claims 29-31, 35 and 44-62 are pending in the application.

Election/Restrictions

Applicants' election of Group III (claims 29-31 and 35), drawn to a method for producing a cell capable of selective genetic diversification of a transgenic target nucleic acid sequence by hypermutation comprising transfecting said target nucleic acid sequence into the immunoglobulin locus of a lymphoid cell, and wherein said lymphoid cell contains no deleterious mutations in genes encoding paralogues and analogues of the RAD51 protein, is acknowledged. The election was made without traverse. Applicants' species election of chicken, hypermutation, immunoglobulin chain, transcription regulatory element, activity of a target nucleic acid on the cell surface, varying the orientation of the gene conversion donors, and RAD54 protein, is further acknowledged. Commensurate with the elected invention, claims 30, 57 and 62 are hereby withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

As the restriction is still deemed proper, the requirement for restriction is maintained and hereby made FINAL. The instant claims have been examined commensurate with the scope of the elected invention and the species of the elected invention. Applicant timely responded to the restriction (election) requirement in the reply filed November 21, 2007.

Claims 29, 31, 35, 44-56 and 58-61 are under current examination.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on September 14, 2006 and March 23, 2007 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the

information disclosure statements have been considered by the examiner, and indicated as such on Forms PTO/SB/8a and PTO-1449.

Objections to the Specification & Abstract

The instant specification is objected to for failure to comply with the requirements of 37 CFR 1.52 (b)(2), requiring (i) Lines that are 1 1 /2 or double spaced; (ii) Text written in a nonscript type font (e.g., Arial, Times Roman, or Courier, preferably a font size of 12) lettering style having capital letters which should be at least 0.3175 cm. (0.125 inch) high, but may be no smaller than 0.21 cm. (0.08 inch) high (e.g., a font size of 6); And 37 CFR 1.52 (b)(5), requiring that the pages of the specification including claims and abstract must be numbered consecutively, starting with 1, the numbers being centrally located above or preferably below, the text.

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see (¶ [0061] of the application publication 2007-0186292). Further, an incorporation by reference by hyperlink or other form of browser executable code is not permitted. See 37 CFR 1.57(d) and MPEP § 608.01. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Failure to Comply with Nucleotide and /or Amino Acid Sequence Disclosures 37CFR §1.821-1.825

37 CFR 1.821 (a) states: Nucleotide and/or amino acid sequences as used in §§1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. 37 CFR 1.821 (d) states: Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Neither the sequences depicted in Figure 3, nor the description of the drawing (¶ [0029] of the application publication), refer to the sequences by SEQ ID NO. The brief description of Figure 3 additionally contains short amino acid motifs, absent corresponding SEQ ID NOS. The instant application may be placed in compliance with 37 CFR 1.821-1.825 by amending either the drawing or the brief description of the drawing to refer to appropriate SEQ ID NOS.

It appears that the instant application does not contain a CRF listing. If the sequences are not present, then new paper and CRF sequences are required.

Claim Objections

Claim 59 is objected to as depending from itself (i.e. claim 59). In the interest of compact prosecution, the claim has been examined as dependent from claim 58.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 29, 35, 44-56, and 58-61 are rejected under 35 U.S.C. 102(e) as being anticipated by Sale et al. (U.S. Patent Application Publication No.: 2005/0026246; filed: Dec. 11, 2003).

The claims encompass a method for producing a cell capable of selective genetic diversification of a transgenic target nucleic acid sequence that is an immunoglobulin chain sequence, by hypermutation, comprising transfecting said target into the immunoglobulin locus of a lymphoid cell capable of gene conversion, wherein said lymphoid cell contains no deleterious mutations in genes encoding paralogues and analogues of the RAD51 protein.

Sale et al. teach a method for generating diversity by preparing an antibody-producing cell line capable of directed constitutive hypermutation of a specific nucleic acid region, comprising selecting a cell in which the rate of V gene mutation exceeds that of other gene mutation (Title and Abstract). Sale et al. state: "directed constitutive hypermutation" refers to the ability of certain cell lines to cause alteration of the nucleic acid sequence of one or more specific sections of endogenous or transgene DNA in a constitutive manner, that is without the requirement for external stimulation ([¶ 0011], p.2). Additionally stating: A "target nucleic acid region" is a nucleic acid sequence or region in the cell according to the invention which is subjected to directed constitutive hypermutation. The target nucleic acid may comprise one or more transcription units encoding gene products, which may be homologous or heterologous to the cell. Exemplary target nucleic acid regions are immunoglobulin V genes as found in immunoglobulin-producing cells ([¶ 0012], p.2 and limitation of claim 29). The authors teach that the nucleic acid which is expressed in the cells of the invention and subjected to hypermutation may be a replacement of the endogenous V region with heterologous transcription unit(s), such as a heterologous V region, retaining the endogenous control sequences which direct hypermutation; or of the insertion into the cell of a heterologous transcription unit under the control of its own control sequences to direct hypermutation, wherein the transcription unit may encode V region genes or any other desired gene product (¶ [0032], p. 3; limitation of claims 44, 50, 51, 53 and 60). Thus, the heterologous transcription unit comprising a target heterologous V region represents a transgenic component of the immunoglobulin locus inserted into the endogenous immunoglobulin locus (a further limitation of claim 29). Additionally teaching: "The plasmids used for delivering the transgene to the cells: are of conventional construction and comprise a coding sequence, encoding the desired gene product, under the control of a promoter. (¶ [0110], p. 7).

A cell capable of directed constitutive hypermutation is taught by Sale et al. as a genetically manipulated chicken DT40 cell (see claim 21, p. 48; limitation of claims 46-49). In Example 8, Sale et al. teach that the generation of sIgM loss-variants in the chicken bursal lymphoma cell line, DT40, can be used to give an initial indication of IgV gene conversion activity; and that compared to the parental DT40 line, a mutant that lacks Rad54 shows a

considerably diminished proportion of sIgM-loss variants ([¶ 0181], p. 14; and limitation of claims 58 and 59). It is therefore evident from the foregoing that a parental chicken bursal lymphoma DT40 cell line is capable of gene conversion (a further limitation of claim 29) and contains the RAD54 gene, without any deleterious mutations in genes encoding paralogues and analogues of the RAD51 protein (a yet further limitation of claim 29). Accordingly, the DT40 cell line is necessarily capable of homologous recombination and DNA repair (limitation of claim 45). DT40 cell lines containing mutations in RAD51 protein paralogues are separately described in ¶ [0182], p. 14.

With regard to the limitation of instant claim 35, for inserting the target immunoglobulin locus by targeted integration, Sale et al. teach: "the endogenous V gene(s) or segments thereof may be replaced with heterologous V gene(s) by homologous recombination, or by gene targeting using, for example, a Lox/Cre system or an analogous technology or by insertion into hypermutating cell lines which have spontaneously deleted endogenous V genes." (¶ [0117], p. 8). Additionally teaching: "The generation of the DT40 derivatives carrying targeted gene disruptions has been described elsewhere. (Bezzubova et al., 1997; Yamaguchi-Iwai et al, 1998; Takata et al., 1998, 2000, 2001)", ([¶ 0186], p. 14; and limitation of claim 61).

With respect to the limitation of claim 51 for using a target nucleic acid encoding a human immunoglobulin V-gene or part thereof, Sale et al. teach: "Clearly, if wishing to extrapolate the approach to allow the *in vitro* production of high-affinity human monoclonal antibodies, it would be advantageous to exploit the genetic tractability of DT40 so as to generate a primary repertoire that includes more than a single V.sub.H/V.sub.L rearrangement." (¶ [0208], p. 18).

Further teaching: "Fluorescence Activated Cell Sorting (FACS) can be used to isolate cells on the basis of their differing surface molecules, for example surface displayed immunoglobulins. Cells in the sample or population to be sorted are stained with specific fluorescent reagents which bind to the cell surface molecules. These reagents would be the antigen(s) of interest linked (either directly or indirectly) to fluorescent markers such as

fluorescein, Texas Red, malachite green, green fluorescent protein (GFP), or any other fluorophore known to those skilled in the art." (¶ [0104], pp. 6-7; limitation of claims 55 and 56).

Therefore by teaching all the limitations of claims 29, 35, 44-56, and 58-61, Sale et al. anticipate the instant invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29 and 31 are rejected under 35 U.S.C. §103(a) as being unpatentable over Sale et al. (U.S. Patent Application Publication No.: 2005/0026246; filed: Dec. 11, 2003), in view of Grawunder et al. (U.S. Patent Application Publication No.: 2006/0052585; filed Dec. 22, 2001).

The claims encompass a method for producing a cell capable of selective genetic diversification of a transgenic target nucleic acid sequence that is an immunoglobulin chain sequence, by hypermutation, comprising transfecting components of said target nucleic acid sequence into the immunoglobulin locus of a lymphoid cell capable of gene conversion, one or more times, wherein said lymphoid cell contains no deleterious mutations in genes encoding paralogues and analogues of the RAD51 protein.

Sale et al. describe a method for generating diversity by preparing an antibody-producing cell line capable of directed constitutive hypermutation of a specific nucleic acid region,

comprising selecting a cell in which the rate of V gene mutation exceeds that of other gene mutation (Title and Abstract). Sale et al. state: "directed constitutive hypermutation" refers to the ability of certain cell lines to cause alteration of the nucleic acid sequence of one or more specific sections of endogenous or transgene DNA in a constitutive manner, that is without the requirement for external stimulation ([¶ 0011], p.2). Additionally stating: A "target nucleic acid region" is a nucleic acid sequence or region in the cell according to the invention which is subjected to directed constitutive hypermutation. The target nucleic acid may comprise one or more transcription units encoding gene products, which may be homologous or heterologous to the cell. Exemplary target nucleic acid regions are immunoglobulin V genes as found in immunoglobulin-producing cells ([¶ 0012], p.2). The authors state that the nucleic acid which is expressed in the cells of the invention and subjected to hypermutation may be a replacement of the endogenous V region with heterologous transcription unit(s), such as a heterologous V region, retaining the endogenous control sequences which direct hypermutation; or of the insertion into the cell of a heterologous transcription unit under the control of its own control sequences to direct hypermutation, wherein the transcription unit may encode V region genes or any other desired gene product (¶ [0032], p. 3). Thus, the heterologous transcription unit comprising a target heterologous V region represents a transgenic component of the immunoglobulin locus inserted into the endogenous immunoglobulin locus. In Example 8, Sale et al. describe that the generation of sIgM loss-variants in the chicken bursal lymphoma cell line, DT40, can be used to give an initial indication of IgV gene conversion activity; and that compared to the parental DT40 line, a mutant that lacks Rad54 shows a considerably diminished proportion of sIgM-loss variants (¶ [0181], p. 14). It is therefore evident from the foregoing that a parental chicken bursal lymphoma DT40 cell line is capable of gene conversion and contains the RAD54 gene, without any deleterious mutations in genes encoding paralogues and analogues of the RAD51 protein.

While Sale et al. do not describe the transfecting a construct containing the target heterologous V region (i.e. a component of an immunoglobulin locus) into the lymphoid cell's immunoglobulin locus containing the target nucleic acid, one or more times, such was well known in the prior art for gene targeting both alleles of immunoglobulin loci in a lymphoid cell.

Grawunder et al. describe a method for the generation of genetically modified precursor lymphocytes, and the use thereof for the production of any heterologous antibody or binding protein (Title and Abstract). In describing the targeting of endogenous gene loci in murine preB cells, the authors state: "For the sequential targeted deletion of both alleles of an endogenous gene locus, two different strategies can be applied. One strategy is to utilize targeting vectors with two different positive selection markers for the targeting of the two different alleles. Alternatively, another strategy is to use the same targeting construct twice for the sequential targeting of both endogenous alleles." (¶ [0250], p. 23).

Grawunder et al. thus provide the motivation to utilize one or more rounds of transfection for gene targeting the immunoglobulin locus of a lymphoid cell with a construct containing a heterologous or transgenic V region.

The references of Sale et al. and Grawunder et al. are both directed to the production of lymphoid cells by gene targeted replacement of endogenous immunoglobulin gene regions with heterologous immunoglobulin gene regions for antibody production. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine their respective teachings and to transfect the gene targeting nucleic acid construct of Sale et al. containing a heterologous immunoglobulin V region into a hypermutating lymphoid cell, by introducing the target nucleic acid sequence one or more times, as described by Grawunder et al., to produce a cell capable of genetic diversification by hypermutation, with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would be motivated to transfect the targeting construct of Sale et al. one or more times, because such would allow the sequential targeting of more than one allele of the immunoglobulin locus of the lymphoid cell.

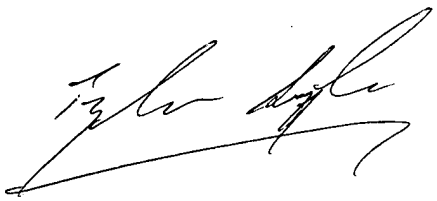
Conclusion

Claims 29, 31, 35, 44-56 and 58-61 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is (571) 272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000. .



Fereydoun G. Sajjadi, Ph.D.
Examiner, A.U. 1633